FASS Federation of Animal Science Societies

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April 6, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Dear Sir:

Enclosed please find comments on Docket # 98D-1146, "A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals" submitted on behalf of the Federation of Animal Science Societies. Should you require any more information, feel free to contact me (301-571-1875; bglenn@faseb.org).

Sincerely,

Barbara P. Glenn

Barbara P. Glenn
Executive Vice President-Scientific Liaison

Enclosure

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Federation of Animal Science Societies
Comments on Docket # 98D-1146,
A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals

Barbara P. Glenn, Ph. D.
Executive Vice President-Scientific Liaison
Federation of Animal Science Societies

Introduction

The Federation of Animal Science Societies (FASS) is a professional organization made up of approximately 10,000 scientists in academia, government and industry which exists to serve society through the improvement of all aspects of food animal production. FASS represents the combined membership of the American Society of Animal Science, the American Dairy Science Association, and the Poultry Science Association.

Use of antimicrobials in farm animals is an important factor in production of healthy animals that result in a nutritious, safe, and economical supply of meat, milk and eggs. Both therapeutic and subtherapeutic uses of antimicrobials are widespread management practices currently impacting the food animal industries. FASS scientists are directly involved on a daily basis with all aspects of the food animal industries through research, development and publication of science based information, technical training, public policy development and technology development and transfer. One goal of our member organizations is the improvement of methods for animal production throughout the United States and other areas of the world. Because of the heavy involvement of our members in animal production, we wish to provide comments on behalf of our entire organization on the Proposed Framework Document, because the concepts and strategies will ultimately affect the role of our scientists as they do their research, teaching, and extension of scientific information. The Framework will also affect the role of our members as they interact with industry and regulatory personnel involved with antimicrobial oversight for the food animal industries. This response represents the position of the FASS Board of Directors and the FASS Committee on Food Safety, Animal Drugs, and Animal Health.

Executive Summary

FASS agrees with the conclusions in the Executive Summary of the National Research Council-Institute of Medicine (NRC-IOM) Committee (1999), that the use of antibiotics in the food animal production system does not appear to constitute an immediate public health concern. We share the concern for public health and recognize the need for further scientific research to fill many of the data gaps identified by the Committee. With new antibiotics and possible new emerging strains of pathogens, some questions are new. We should learn from past experiences and carefully look at new situations while research provides information not totally available at the current time. To

not act if some of the concerns turn out to be real is not justified. Likewise, to take actions that are not warranted also can be very costly to both livestock producers and consumers.

Comments

Nearly 60 % of all antimicrobials used in the United States are used in human medicine. The remainder is used in food-producing and companion animals. While therapeutic levels of antimicrobials are used after diagnosis for treatment of disease for improvement of animal health, subtherapeutic use of antimicrobials in feed or water improves animal health, growth rate and feed efficiency, and reduces mortality and morbidity. Subtherapeutic use of antimicrobials as low level supplementation in food-producing animals has been done since 1951. Some of the antimicrobials used both therapeutically and subtherapeutically are also used in human medicine.

FASS shares the concern with the Food and Drug Administration (FDA) for the potential development of antimicrobial resistance from the use of antimicrobial drugs in food animals. We support the role of the FDA in ensuring that the use of antimicrobial drugs in food-producing animals does not result in adverse health consequences to humans. The Proposed Framework is based on the premise that development of antibiotic resistance in enteric bacteria will occur, and when antimicrobial drugs are administered to food producing animals, they can thus promote the emergence of resistance in bacteria that may not be pathogenic to the animal, but may be pathogenic to humans.

We agree that microorganisms can mutate to develop or acquire resistance to antibiotic drugs in several ways, based on the scientific literature. However, FASS does not agree with the assumption that use of antimicrobials in food-producing animals plays a significant role in selecting for resistance in foodborne pathogens which consequently may be passed to humans and adversely impact public health. **We believe that the Proposed Framework is does not scientifically validate the issue of resistance transfer. The FDA should not go forward with the Proposed Framework regulatory approach until there is verified scientific data to support the premise of a direct link between antimicrobial resistance in foodborne pathogenic bacteria in humans and the use of antimicrobials in food-producing animals.**

The National Research Council-Institute of Medicine Document

Based on the concerns indicated, the U. S. Department of Agriculture (USDA) and the Center for Veterinary Medicine (CVM) of the FDA asked the National Research Council (NRC) to form a committee to examine and review the benefits and risks associated with drug use in the food animal industry. The NRC assigned the task to the Board on Agriculture, which, through the Panel on Animal Health, Food Safety, and Public Health- a joint panel with the Institute of Medicine (IOM)- convened the Committee on Drug Use in Food Animals. Their report, "The Use of Drugs in Food Animals, Benefits and Risks" was published by the NRC in 1999. Before final decisions are made to consider increased requirements for evaluating new antimicrobials for use in farm animals, there are several findings of the review conducted by this esteemed committee

which should be reviewed. **FASS supports the recommendations of the NRC-IOM Committee and interprets their findings as indicative of the current status of use of antimicrobials in food-producing animals. We believe that their conclusions are being overlooked by the FDA and should be re-visited by the FDA prior to any increased regulatory requirement.** Therefore, we have reviewed the pertinent findings of the NRC-IOM Committee. The bottomline question: Is there scientific data to warrant increased requirements outlined in the Proposed Framework Document?

Comments of the NRC-IOM Committee in Executive Summary (1999)

The NRC-IOM Committee noted that use of antibiotics increases the risk of emergence of microorganisms that are resistant to specific antibiotics, as well as those with similar biological mechanisms. "Development of this kind of resistance is not restricted to antibiotic use in food animals; it is far more prevalent because of misuses in human medicine." (NRC-IOM, 1999, p. 7)

The NRC-IOM Committee noted that emergence of resistance in bacteria in animals that receive antibiotics is related to the concentrations of the drugs to which bacteria are exposed and also to the duration of treatment or exposure, and that there are no clear definitions of the duration or dosage at which resistance develops (p. 7). They recommended that resistance emergence should be classified with regard to each antibiotic used, the concentration and dosage administered, the blood and tissue concentrations attained, the bacterial species or strain affected, and the animal species in which the drug is used. Furthermore, the committee stated "A specific data-driven link should be available to substantiate that the use of an antibiotic at a particular dosage not only promotes resistance but also poses a disease threat to other animals or humans." (NRC-IOM, 1999, p. 7)

The NRC-IOM Committee further concluded that substantial information gaps contribute to the difficulty of assessing the effect of antibiotic use in food animals on human health (p. 8-9).

"First, it is unclear that the observed or perceived increase in transference of antibiotic resistance to humans are associated with the use of antibiotics in the food-animal industry."

"Second, there are no scientific data on resistance emergence and pathogen transfer in situations in which a therapeutic drug intervention is prescribed during subtherapeutic drug use for growth promotion that began in the absence of disease and when no prior disease state existed."

"Third, there are only sparse data to relate the dosages of a drug necessary to foster resistance to those dosages used and the observed degree of resistance."

"Fourth, antibiotic use is an integral part of the food-production system in the United States, and it is effective in enhancing growth."

"Fifth, the detection of antibiotic-resistant microorganisms in treated animals does not automatically imply the presence of disease; many drug-resistant bacteria are not pathogens."

"Sixth, human oral antibiotic use might predispose some parts of the population to

increased susceptibility to enteric clinical infection with food-animal enteric pathogens; there are few data for assessing how genes that code for resistance in bacteria move among and between bacterial species, and there is no concrete information on whether or how nonpathogenic bacteria exposed to antibiotics participate in the resistance emergence phenomenon."

The NRC-IOM Committee finalized comments by saying that until these questions are answered definitely, the quest for new antibiotics for use in food animal must continue, including use of alternatives to antibiotics for maintaining health and productivity (p. 9).

NRC-IOM (1999) Conclusions and Major Recommendations

The NRC-IOM Committee concluded that a review of the use of antimicrobials in the food-animal production industry as related to potential for effects on human health was warranted:

"The committee concludes that the use of drugs in the food -animal production industry is not without some problems and concerns, but it does not appear to constitute an immediate public health concern; additional data might alter this conclusion." (NRC-IOM, 1999, p. 9).

The NRC-IOM Committee called for a science-driven decision-making process:

"The committee recommends establishment of integrated national databases to support a rational, visible, science-driven decision-making process and policy development for regulatory approval and use of antibiotics in food animals, which would ensure the effectiveness of these drugs and the safety of foods of animal origin." (NRC-IOM, 1999, p. 11).

The NRC-IOM Committee called for interdisciplinary oversight in development and use of antibiotics:

"The committee recommends that further development and use of antibiotics in both human medicine and food-animal practices have oversight by an interdisciplinary panel of experts composed of representatives of the veterinary and animal health industry, the human medicine community, consumer advocacy, the animal production industry, research, epidemiology, and the regulatory agencies." (NRC-IOM, 1999, p. 11).

The NRC-IOM Committee concluded that additional research must be conducted:

The committee recommended "increased funding for basic research that explores and discovers new or novel antibiotics and mechanisms of their action". (NRC-IOM, 1999, p. 10). They recommended increased research on "the effect of nutrition and management practices on immune function and disease resistance in all species of food animals." (NRC-IOM, 1999, p. 11). Furthermore, they recommended further research on strategies for "the development of new vaccination techniques, on a better understanding

of the biochemical basis of antibody production, and on genetic selection and molecular genetic engineering for disease resistance." (NRC-IOM, 1999, p. 11)

The Proposed Framework if Implemented

In our public comment at the meeting of the CVM Advisory Committee on January 25-26, 1999, FASS stated that the issue of monitoring microbes to judge the development of resistance may be more complicated than it might seem. There are several questions for which answers are not obvious in the Proposed Framework. One central question that must be answered is "What is the definition of resistance?" Is it just any increase in dose required to inhibit organisms, or is it the total resistance to previously effective antibiotic? How many samples are needed to provide assurance of real changes due to antibiotics versus random changes that occur over time?

In addition, there are practical concerns regarding a new regulatory framework that might decrease further the approval of new antimicrobials. Implementation of such a regulatory framework will be costly: in impaired animal health, in the potential loss of the safe healthful food supply as we now know it, in the increased cost to livestock producers, and in the increased cost to the consumer. The economic cost of eliminating subtherapeutic use of antibiotics was estimated by the NRC-IOM Committee (1999, p. 184) – "The committee's conclusion is that the average annual per capita cost to consumers of a ban on subtherapetic drug use is $4.84 to $9.72. .....assuming a U.S. population of 260 million, the total amounts to about $1.2 billion to $2.5 billion per year."

The Proposed Framework relies on the previous Guidance Document (63 FR 64094) which concluded that microbial safety included measurement of both 1) pathogen load; and 2) resistance. The Proposed Framework proposes to assess the effect of proposed use of an antimicrobial on human pathogen load; assess safety of proposed antimicrobials according to their importance in human medicine; assess pre-approval data on resistance transfer; establish "resistance" and "monitoring" thresholds; and establish post-approval studies and monitoring. These approaches were espoused as the best thinking of the CVM on this subject. However, the NRC-IOM Committee clearly does not agree with the need for an increased regulatory approach, based on their review of the scientific literature. Prudent use principles were supported. Although a postulated hazard has been identified again, the relative risk to public health must still be assessed.

Executive Summary

FASS agrees with the conclusions of the NRC-IOM Committee (1999), that the use of antibiotics in the food animal production system does not appear to constitute an immediate public health concern. We share the concern for public health and recognize the need for further scientific research to fill many of the data gaps identified by the Committee. With new antibiotics and possible new emerging strains of pathogens, some questions are new. We should learn from past experiences and carefully look at new situations while research provides information not totally available at the current time. To not act if some of the concerns turn out to be real is not justified. Likewise, to take actions

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Reference:

National Research Council-Institute of Medicine. 1999. The Use of Drugs in Food Animals, Benefits and Risks. National Academy Press, Washington, DC.

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